REMARKS

Status of the Claims

Claims 26, 27, 30, 32-35, and 37-45 are pending.

Claim 26 has been amended. Support for the amendments is found on page 11, lines 25-28, page 12, lines 5-14 and 28-31, page 13, lines 8-11 and 18-20, page 14, lines 1-3 and 10-12, page 17, lines 23-25, and page 18, lines 3-4.

Claim 44 has been amended in order to adequate the dependence of claims.

No new matter has been added.

1. Claim rejections under 35 USC §112 Written Description

The Examiner rejects claims 26-27, 30, and 32-35 as failing to comply with the written description requirement. The Examiner states that support for the weight percentages during the method is lacking because Applicants referred to percent weights which were to final percent weight.

The Examiner's written description rejection relates to whether one of skill in the art at the time of filing would have understood Applicants to have had possession of a process for preparing compositions comprising 10% to 50% w/w of ritonavir. The claims have been amended to recite a final concentration of ritonavir in the body of the claim. The final concentrations of the other components have been recited in the claim as well. Amended claim 26 specifies that the amount for the components used during the process of making in %w/w is a percent of the weight of the final composition.

Contrary to the Examiner's understanding, the percentage weights during the process are exactly the same of the final product percentage weights. The examples of the application as filed show that the desired final amounts of the composition ingredients are the same of those added during the manufacturing process with the exception of the ethanol (which is evaporated after the dissolution and filtration steps to the desired amount in the final composition), adjusting agents, and water amounts.

Specifically with regard to the ritonavir amount, the Applicants explain that there is no contradiction in "completely dissolving ritonavir" and subsequently "filtering the solution to retain microparticles" without affecting significantly the initial amount added of ritonavir, once ritonavir dissolves totally in the initial amount of ethanol (higher than the ethanol weight in the final composition).

Applicants emphasize that the condition to finish the first step of the claimed process is **obtaining a completely clear solution** by dissolving ritonavir in a sufficient quantity of ethanol to do so (See the Specification at page 17, lines 23-25: "ritonavir is completely dissolved in a sufficient quantity of the alcoholic solvent, preferably ethanol, in order to obtain a completely clear solution...").

One of skill in the art is aware that a clear solution obtained by a complete dissolution of a solid into a solvent, as occurs in the present case, can be filtered without loss of the dissolved solids. The filtration is to remove any possibly existing microparticles that are not visible in the solution and do not have significant weight, but would be sufficient to trigger the precipitation of ritonavir. Contaminant solid particles which are not ritonavir, may trigger its precipitation as well, and thus, the filtration also removes them. (See the Specification at page 17, lines 28-31: "To guarantee the absence of solid particles that can trigger the precipitation process later, this alcoholic solution is filtered using usual filtration techniques...".)

Therefore, the filtration step plays an essential role in the stability of the final composition, without material alteration of the ritonavir content in the final product. This is one of the inventive features of the instant process.

Secondly, the tests made with the preferred compositions of the present invention shown at the pages 35-38 of the Specification as filed confirm the Applicants' foregoing statements, specifically with regard to the initial and final assays values, which are not significantly different from one to another. These data are presented in the Table on pages 36 and 37.

Applicants agree with the Examiner that the initial amount of ethanol, and only of this starting material, is greater than its final amount in the composition. Due to this essential practical condition, the process requires the steps (c), (e) and (g) to adjust the

desired final amount of ethanol in the final composition. If the process is not carried following the steps described in claim 26, one cannot obtain the final composition in form of a stable solution of ritonavir. Applicants emphasize that the inventive step is not in diminishing the ethanol volume through the distillation, but instead it is in using the whole process (including all its steps) to obtain a stable and concentrated ritonavir composition.

The Examiner rejects claims 26-27, 30, and 32-35, as failing to comply with the written description requirement. The Examiner states that there is no support for the term "excess amount of an alcoholic solvent of C_2-C_4." Applicants have amended the claim so that it no longer recites "excess." Furthermore, the Specification discloses that "[r]itonavir was dissolved in an enough amount of ethanol to [achieve] its complete dissolution at a temperature between 30 and 45°C." (Specification page 22, lines 17-18). As discussed above, one of skill in the art would recognize from this disclosure that the amount of alcohol needed to dissolve a given amount of ritonavir is result based, and this is not indefinite.

Moreover, one of skill in the art reading the Specification would recognize that Applicants had possession of a method including adding enough alcohol to an amount of ritanovir (from 10% to 50% w/w of the final composition) to dissolve all of the ritonavir; such is disclosed at page 17, lines 23-31 of the Specification.

Since it is plain that the present Specification describes the presently claimed method in a clear manner commensurate with the scope of the present claims, the instant rejection should be withdrawn.

2. <u>Claim rejections under 35 USC §112 - Indefiniteness</u>

The Examiner rejects claims 26-27, 30, and 32-35 under 35 USC § 112, second paragraph as indefinite. The Examiner states that "the methods of manufacture steps do not state a specific concentration, weight, or final product form as an endpoint." Applicants respectfully disagree.

Applicants point out that claim 26 already recited "A process for preparing compositions comprising 10% to 50% w/w of ritonavir..." Therefore, the final product is a

composition comprising 10% to 50% w/w of ritonavir. Applicants submit that one of skill would have understood what is claimed based on that recitation. However, to ensure clarity, Applicants have amended claim 26 to add the final concentration of ritonavir into the body of the claim to better define the metes and bounds of the claim.

With regard to the other ingredients, Applicants have also already added the concentrations of them to the claims with the Amendment dated June 3, 2008; the recited concentrations being the endpoint and specific weights well defined. The presented amounts in % w/w are a percent of the weight of the final composition.

The Examiner rejects claims 26-27, 30, 32-35 as indefinite because "the term excess amount is also unclear as to how much solvent is used." As discussed above in the Written Description section, claim 26 no longer recites the "excess amount" language.

Besides, one of skill in the art would recognize that it is not necessary to recite a specific volume of the solvent in the dissolution step to make it well defined. Once stating a solute and its solvent, the relation between them establishes a "sufficient amount" to dissolve the solute through the property of the solubility of the solute. Thus, the term "sufficient amount" is not indefinite.

Applicants submit that the amendments to claim 26 obviate the rejection, and request that the rejection be withdrawn.

3. Claims rejection under 35 USC §103

3 (a). Lipari et al (US Patent 6,232,333) in view of Bailey et al (US Patent 6,008,228)

The Examiner rejects claims 37-45 under 35 USC § 103(a) as being unpatentable over Lipari in view of Bailey.

The Examiner asserts that

> The arguments in [with] regards to Bailey is [are] not commensurate in scope with the rejection as the Bailey reference was used to show the teaching that incorporation of the monoglycerides ... assist in alleviating the inadequacies of hydrophobicity and absorption.... The arguments are directed to the entire formulation in Bailey and the examples for saquinavir. The primary reference is Lipari which addresses the formulation, not Bailey....

(Office Action dated August 21, 2008 page 13).

Applicants submit that their arguments were directed to Bailey because the Specification discloses that the Bailey composition "is inadequate to supply stable composition of ritonavir" (Specification, page 8, line 13-14).

The Pacheco Declaration

The Examiner dismisses the Pacheco Declaration (submitted with the Amendment dated June 3, 2008) as not relevant to the present rejection because "[t]he declaration goes to the formulation of Bailey and not the formulation of Lipari which is presented in the rejection." However, a declaration of unexpected results should compare the invention and the closest prior art. *In re Baxter Travenol Labs.*, 952 F.2d 388, 392, 21USPQ 1281 (Fed. Cir. 1991). Applicants explained that Lipari was not the closest prior art because Lipari teaches long chain fatty acids as the most plentiful ingredient of the composition and does not teach the process steps of the present invention. (Declaration, page 2, section (I) and [0058]). The instant invention does not employ any type of fatty acid.

Contrary to the Examiner's understanding, the Applicants emphasize that the Lipari's long chain fatty acids are not equivalent to the present invention medium chain mono/diglycerides.

The fatty acids of Lipari's document are those that are *liquid at room temperature* (column 8, lines 21-22) and their structures must comprise long chain of carbon atoms (C_{12}-C_{18}). On the other hand, the mixture of mono/diglycerides employed in the instant invention is in the form of *semi-solid liquid at room temperature* and comprises medium-length chains of carbon atoms (C_8-C_{10}). Furthermore, glycerides are esters and fatty acids are carboxylic acids presenting distinct physical-chemical properties. Such diverse properties make these ingredients very different, and thus, not equivalent in the field of pharmaceutical formulation.

Therefore, and especially when dealing with a highly insoluble active ingredient as ritonavir, one of skill in the art would not consider glycerides and fatty acids as routinely substituted.

The Examiner states that "judgment of obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. **But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper.**" However, the Examiner's interpretation that Bailey would suggest the substitution of the Lipari's fatty acids for a mono/diglycerides mixture is a hindsight reconstruction of the claimed invention based on the disclosure provided by the Applicants. For example, the Examiner fails to explain why one of ordinary skill in the art would choose to use a neutral ester (Bailey) rather than a charged fatty acid (Lipari) in the composition. One can only presume that the reason is the teaching of the Applicants' disclosure, since Bailey teaches a saquinavir composition and, as asserted in the Pacheco Declaration, such composition and method for preparing the same are totally inadequate to be applied for ritonavir for the reasons set forth in the Declaration.

Even supposing that at the time the present application was filed the skilled artisan would have the expectation that mono/diglycerides are adequate to provide a ritonavir composition by direct dissolution of ritonavir in this solvent, the instant Specification and the Pacheco Declaration show a contrary result.

The Examiner's dismissal of the Declaration as not relevant to "the formulation of Lipari which is presented in the rejection" is not proper. The Declaration proves that a mixture of the same ingredients of the claimed composition, which the Examiner considers to be the combination of Lipari and Bailey, does not become a clear solution if prepared by a method of "direct dissolution of ritonavir into the mixture of the excipients with heating until 30-45°C. (Declaration [0014], [0031]-[0034]). Both Lipari and Bailey teach direct dissolution of ritonavir into the mixture of excipients.[1] Because the mixture of the ingredients of the presently claimed composition when made by another method does not result in the claimed composition (i.e., a clear, stable solution), the Applicants have

[1] For instance, Bailey teaches heating of the monoglycerides, antioxidant, and PVP to 55-60°C and addition, mixing, and dissolution of the previously "sieved" proteinase inhibitor in the monoglycerides/ antioxidant/PVP solution. (See Bailey, Example 1). Lipari teaches mixing alcohol and oleic acid while "warmed" between 28-37°C, warmed "as necessary", or at 23-33°C, and then adding the antioxidant, castor oil, and ritonavir. (*See e.g.*, Lipari, Examples 7, 9, 10, 29)

overcome the Examiner's obviousness rejection with regard to the composition, and to the process of making the same.

Polymorphs

The Examiner also states that "the declaration is also not commensurate in scope with the claims as the declaration and comparative goes to polymorphs which are not presented in the claims or the Specification…".

Applicants wish to point out that the "polymorphs" are disclosed in the Specification, for instance, at page 5, lines 18-26, continuing to page 7; at page 15, line 24 up to page 16, line 23; and page 18, line 26, up to page 19, line 27.

In fact, the possibility to dissolve both known crystalline forms of ritonavir (polymorphs) is another inventive feature of the present application. Contrarily to the state of the art formulation (Lipari), (See page 7, lines 28-32, continuing to page 8, lines 1-5 of the present filed application), the present invention composition and the process for making the same permit working with both polymorphs without re-precipitation, as disclosed in the Specification and in the Pacheco Declaration.

Comparison of Monoglycerides

The Examiner also dismisses Applicants' arguments comparing the amount of monoglycerides in the formulation of Bailey and the amount found in the present composition. The Examiner suggests that the use of IMWITTOR as disclosed in Bailey would be the equivalent of the amount of monoglycerides in the presently claimed composition. Applicants respectfully disagree.

First, Bailey teaches that the total amount of monoglycerides in the final composition is 40-80%. When AKOLINE is at its highest claimed concentration, the maximum amount of mono/diglyceride mixture (total) is at 40%. (Claim 10). That means that the presently claimed composition has a maximum of 24.8% monoglycerides, where Bailey would have minimum amount of 40% monoglycerides. (See table below). Thus, one of skill in the art, attempting to determine optimum and operable conditions would not have arrived at the range 20-40% mono-di-glycerides because Bailey teaches that the amount of

monoglycerides alone is at least 40%, and the amount of the combined glycerides would be a significantly higher percentage of the total composition.

	Monoglyceride Content of the mono/diglyceride solution	**Diglyceride Content of the mono/diglyceride solution**	**Total amount of monoglycerides in the final composition**
INWITTOR	50%	40%	40-80% (Bailey's reference)
CAPMUL MCM or CAPMUL MCM 90	70% (but generally 83-95%)	30% (generally 5-17%	40-80% (Bailey's reference)
AKOLINE	50-32%	38-40%	10-12,4% monoglycerides when AKOLINE is 20% of final composition (as disclosed in the present application)
AKOLINE	50-62%	38-40%	20-24,8% monoglycerides when ALKONINE is 40% of the final composition (as the limit specified in claim 10 of the present application)

3 (b). Lipari in view of Bailey and CU Boulder Organic Chemistry Undergraduate Courses, Lab Techniques.

The Examiner rejects claims 26, 27, 30, and 32-35 as unpatentable over Lipari in view of Bailey as applied to claims 37-45 and further in view of CU Boulder Organic Chemistry Undergraduate Courses, Lab Techniques.

First, the Examiner's conclusion that the claims do not recite complete dissolution, that the filtration is contrary to complete dissolution, and that there is allegedly no endpoint is discussed above in the written description/indefiniteness sections. Applicants submit that the Examiner has misinterpreted the claims to arrive these conclusions.

Second, Applicants submit that the consideration that vacuum distillation is a known technique in not conclusive on the obviousness issue. Although it is a usual technique, the employment of vacuum distillation in the instant process to achieve concentration of the ritonavir solution is not an obvious step. One of skill in the art would

expect that the evaporation of the solvent could lead to re-precipitation of ritonavir due to its known instability within a solution. Since such precipitation does not occur in the method of the present invention (or from the resulting composition), the invention must be acknowledged as providing a result not expected by one of ordinary skill in the art who reads the references cited by the Examiner.

The evaporative concentration step is a part of an inventive ritonavir dissolution technique which is inserted into a new whole process configuring a new and inventive way to prepare concentrated and stable ritonavir compositions. The claimed process as a whole has never been taught or suggested by others at the time the invention was made.

Besides, the claimed process solves a long lasting prior art problem. In the case of the present application:

1. Prior art problem: ritonavir low solubility and impossibility to make more concentrate composition due to high instability of the ritonavir within the solutions;

2. Prior art attempts: finding an adequate solvent, or mixture of solvents which, at the time of the present invention, showed to be viable only to a limited concentration of ritonavir;

3. Present invention solution: disclosure of a process which includes new dissolution technique capable to eliminate the origin of the ritonavir instability and wherein one of the special features of the new dissolution technique is the employment of vacuum distillation which had no expectation of being successful.

Third, the Examiner's conclusions regarding the "polymorphic" forms of ritonavir simply ignores the entire point of the Declaration. The Declaration uses the polymorphic forms to show that the method works with both forms of ritonavir and is an improvement over the prior art. Also, the Examiner's statement that dissolved compounds are not polymorphic is not relevant because the polymorphic form affects directly the dissolution process and the stabilization of the final solution.

In the present case, the method is directed to whether ritonavir dissolves in a given solvent and stays dissolved. Unlike the prior art, the solution obtained from the present method can be obtained from the less soluble polymorph without excessive heating and is stable at room temperature. (See Specification, pages 19, lines 3-32).

The Specification discloses that there are polymorphic forms of ritonavir and that one is less soluble than the other. (Specification, page 5, line 24-26). The Specification also discloses that a concentrated solution of ritonavir is not stable when obtained by methods of the prior art. (See Specification, page 7, line 31-32; page 8, line 12-13).

Furthermore, the Pacheco Declaration clearly shows that both the more soluble and the less soluble forms of ritonavir do not completely dissolve when added directly to the excipients. (Declaration [0014], [0031]-[0034]). Moreover, the method as disclosed in the Declaration shows that a composition having the same ingredients as the present composition does not completely dissolve by direct addition of the ingredients at the low temperature showing that the teachings of Bailey and Lipari are not enough to successfully make the compositions of the present invention. (See Declaration [0017]-[0021], [0033]-[0039], Figure 9, panels A, D and E). Thus, Applicants submit that the Examiner's rejection is overcome by the evidence in the Specification and in the Declaration. Applicants request that the rejection be withdrawn.

4. Conclusion

In view of the foregoing amendments and remarks, Applicant respectfully request immediate allowance of the claims, which define subject matter that meets all statutory patentability requirements.

If the Examiner has any questions or comments, please contact the undersigned by telephone to discuss the matter.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17, particularly, extension of time fees.

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